

US EPA ARCHIVE DOCUMENT

5173

Study: SC-0224 Two-Generation Reproduction Study in Rats

Laboratory: Environmental Health Center
Stauffer Chemical Company
Farmington, Connecticut

Study No. and Date: T-11051, April 19, 1984

Accession No.: 258398 (Appendix 8), 258399

Material Tested: Aqueous SC-0224 technical containing 19.2% active ingredient by weight.

Animals: Rat [Crl CD (SD)Br]

The purpose of this study was to determine if SC-0224 technical has effects on rat reproduction when administered in the diet.

Materials and Methods: (as paraphrased from Study Procedure)

Husbandry: Standard GLP

During mating, one male was housed with one or more females. Subsequent to mating, females were individually housed. On gestational day 20, pregnant females were transferred to larger cages for delivery and weaning. Weanling pups were subsequently housed two per cage. At approximately 40 days of age pups were housed singly for future breeding.

A. Experimental Design (Excerpted from Study No. T-11051, pp. 2-9)

Following quarantine, "80 males and 120 females were assigned to four dose groups of 20 males and 30 females each. Beginning at 43 days of age the animals were fed purified rodent meal containing 0, 150, 800, 2000 ppm of active SC-0224. At the end of 62 days of treatment, 105 days of age, the 20 males and 30 females of each group were randomly mated to yield the litters of the Fla generation. Fla pups were weaned at 21 days and discarded. At 160 days of age, study day 118, P0 animals were randomly mated a second time to yield the Flb litters. On postpartum day 4, Flb litters were culled to eight pups (where applicable) leaving, as nearly as possible, four males and four females per litter. The culled pups were necropsied under the supervision of the Study Director. Following weaning, 20 male and 30 female weanlings of each group were randomly selected and continued on their respective treatments as the P1 animals. Additionally, five male and five female

copulatory plug were detected was considered day 0 of gestation. The cohabitation period was 24 hours/day for up to three weeks. Weekly body weights were continued on males and unmated females.

3. During the Gestational Phases

Body weights were taken on gravid days 0, 6, 13, and 20. Food consumption was determined for the gravid day intervals 0-6, 6-13, and 13-20.

4. During the Perinatal Phases

On gravid day 20, females were transferred to a large cage. Beginning on day 21, the females were monitored for normal behavior in the sequence of events during parturition. Following delivery, the dam and litters were examined as soon as possible. The day of delivery was considered postpartum, or lactational, day 0. Deliveries beginning before 3:00 p.m. were assigned that calendar date; those after, the next calendar date.

5. During the Lactational Phases

The dam and litter were examined after the dam had cleaned and assembled the litter; usually on day 0, but occasionally on day 1. On lactational days 0 or 1, 4, 7, 14, and 21 the dam body weight, total litter size, numbers of live and dead pups, and pup anomalies were recorded. For Fla and F2a litters, the total live litter weight was taken on days 0 or 1, 4, 7, and 14, and individual pup sexes and weights were recorded on day 21.

Flb and F2b litters were given more extensive examinations. On day 0 or 1, pups were sexed individually, but weighed collectively. Individual pup sexes and weights were recorded on days 4, 7, 14, and 21. The litters were culled on day 4 to eight pups leaving, when possible, four males and four females in each litter. In addition, on the day indicated, completion of the following maturational landmarks were determined for the pups: day 4, unfolding of the external pinna of the ear; day 7, incisor eruption; day 14, opening of the eye. At each weighing before day 14, the presence or absence of milk in the stomach of the pups was noted.

<u>Organ System</u>	<u>Tissue</u>	<u>Fixative*</u>
Digestive (cont'd)	Rectum	NBF
	Pancreas	NBF
	Liver	NBF
Urogenital	Kidneys	NBF
	Urinary bladder	NBF
	Testes	BG
	Epididymides	BG
	Prostate	NBF
	Seminal vesicles	NBF
	Coagulating glands	NBF
	Ovaries	BG
	Vagina	NBF
	Cervix	NBF
	Uterus	NBF
Endocrine	Pituitary	BG
	Thyroids	NBF
	Parathyroids	NBF
	Adrenals	BG
Nervous	Brain	NBF
	Sciatic nerve	NBF
Special Senses	Eyes	BG
	Harderian glands	BG

Gross lesions (as specified
by the pathologist)

- b. Necropsies without Organ Weights or Tissue Collection: After carbon dioxide asphyxiation, both the F1b and F2b pups culled on day 4 and those not selected for either organ weight determination or the next parental generation on day 21 were necropsied under the supervision of the Study Director. The heads of culled pups were fixed in Bouin's fixative and then examined by free-hand razor blade sectioning according to Wilson (1965). The thoracic and abdominal viscera were examined according to Staples (1974).

*BG - 2.5% buffered gluteraldehyde, NBF - 10% neutral buffered formalin.

"2. Unscheduled Terminations

- a. Parental Animals: Moribund animals which were sacrificed and animals which were found dead were necropsied under the supervision of a Veterinary Pathologist.
- b. Preweaning Pups: Preweaning Flb and F2b pups which died and stillborn pups were necropsied under the supervision of the Study Director. The heads of these pups were fixed in Bouin's fixative and examined according to the method of Wilson (1965). The thoracic and abdominal viscera were examined by the technique of Staples (1974)."

Data Interpretation

"1. Parameters

In addition to the raw data collected, other parameters were calculated and analyzed statistically, these parameters are defined in the tables.

"2. Statistical Analysis

Quantitative or continuous data such as body weights, feed intakes, pup weights, and organ weights were tested for significance using a one-way analysis of variance and Dunnett's procedure (Dunnett, 1964).

Enumeration data for each group, including clinical observations, necropsy findings, reproductive counts, and weanling findings were evaluated using the Fisher exact probability test (Siegel, 1965) with Bonferroni's correction for multiple comparisons to a control value (Ingelfinger, 1983).

Additionally, litter parameters including the number of male, female, and viable pups and litter incidences such as the live-born index, survival indices, and developmental landmarks were analyzed with a nonparametric rank test (Mann-Whitney U, Steel, 1960).

Fisher exact tests were one-tailed. All other tests were two-tailed. Statistical significance was based on a level of $p < 0.05$, but values also significant at $p < 0.01$ were so indicated." (pp 2-8)

in the 2000 ppm group from day 62 essentially to the end of the study during which time four of ten weight determinations were significantly reduced. For the P1 females, weight gain was inhibited in both the 800 ppm and 2000 ppm groups throughout the study period, whereas the reductions for most determinations were statistically significant (Tables 23 and 24, pp. 90 to 94). There were no consistent dose-related effects on food intake for P0 females. Among P1 females, food intake was significantly reduced for the first 62 days of observation, however, this effect was not apparent on days 118 to 191 (Tables 25 and 26, pp. 95 to 98). Thus in summary, for reduced weight gain:

P0 male LOEL	=	800 ppm
female LOEL	=	2000 ppm
P1 male LOEL	=	800 ppm
female LOEL	=	800 ppm

C. Feed Efficiencies

Feed efficiencies for P0 and P1 male and female rats (premating) were unaffected by dosing (Tables 9 and 10, pp. 50 to 56 and Tables 27 and 28, pp. 99 and 100). There were some puzzling numbers in Table 9. For example, at 84 days (p. 51) figures for the 0, 150, 800 and 2000 ppm groups were, respectively, -258, -15, -66, and 10.

D. SC-0224 Intake

Generally speaking, with respect to actual SC-0224 intake, it was observed that for P0 and P1 males, intake declined from the initial time point (day 8) to the time of mating (day 62) and then remained fairly constant. Overall mean intakes were 0, 6.2, 35, and 85 mg/kg/day for P0 males and 0, 6.1, 35, and 92 mg/kg/day for P1 males. At the time of mating, the values of P0 females were 0, 9, 43, and 101 mg/kg/day and 0, 7, 39, and 95 mg/kg/day for P1 females.

E. Necropsy - P0, P1

Necropsy of P0 and P1 males did not disclose any unusual findings or increased incidence of adverse effects at any dose level (Tables 13 and 14, pp. 64 to 67). Similarly, necropsy findings for P0 and P1 females did not disclose any remarkable effects of SC-0224 at any dose level (Tables 31 and 32, pp. 103 to 107).

Absolute organ weights for P0 males were generally unaffected by SC-0224. A notable exception was that of the thymus, which was significantly reduced in the high dose-group (0.339 gm vs. 0.500 gm [control]). Among P1 males a number of organ weights were significantly reduced in the

times. These changes may be the consequence of dosing and as the study authors indicate elsewhere may be related to palatability of the food, SC-0224 admixture (Tables 45 to 48, pp. 128 to 131). Data provided on food efficiency and SC-0224 intake during gestation did not disclose any points of appreciable concern.

H. Dam Weights During Lactation

Dam weights for postpartum days 4 to 21 were significantly reduced in the high dose group of P0 generation, 1st mating. The dam weight was not significantly reduced for this group at time 0. Dam weight of generations P0 (2nd mating) and P1 (1st and 2nd matings) for the 800 ppm and 2000 ppm dose groups were significantly less than control weights during the 0 to 21 days of lactation (Tables 57 to 60, pp. 140 to 143).

I. Dam Food Intake During Lactation

Generally, food intake, as measured during lactation days 4 to 21, was significantly reduced for both matings of the P0 and P1 generations in the high-dose group. There was some evidence of food intake reduction in the 800 ppm dose groups, particularly in the P1 generation (2nd mating), where at three of the four postpartum time points food intake was significantly reduced (Tables 61 to 64, pp. 144 to 147).

Food efficiency and SC-0224 intake data reported during lactation did not provide any remarkable findings.

II. LITTER AND PUP PARAMETERS

A. Litter Size

Mean litter size was significantly reduced in the 2000 ppm dose group of the P0 first mating. The mean litter size at birth was 10.5 ± 3.2 for the 2000 ppm dose group as compared to 12.5 ± 2.3 for the control group. By virtue of this at birth reduced litter size for the 2000 ppm group, litter size on live days 0 to 21 were in general significantly reduced. However, there was no evidence of increased pup mortality in this or any other dose group during the 21-day postpartum period. For P0 (2nd mating) and P1 (1st mating), mean litter sizes were not altered at any dose level, at birth or during 21-days postpartum. For P1 (2nd mating), there were two live day time points (0 and 4 days) where litter size was reduced in the high-dose group. This was not true at later time points. These significant reductions may simply reflect

Surprisingly, in the P1 (2nd mating), mean pup weight at birth was unaffected by dosing. Furthermore, mean pup weights were not altered on postpartum day 4 or 7. On postpartum days 14 and 21, mean pup weight was significantly reduced in the 800 ppm and 2000 ppm dose groups. This inhibition was of greater magnitude in the 2000 ppm group than in the 800 ppm group (Tables 77 to 80, pp. 160 to 163).

C. Pup Survival and Development

Among offspring of the first and second matings of the P0 and P1 generations, there were no adverse effects of dosing evident with respect to the following parameters: liveborn index, viability index, lactation index, survival indices. Furthermore, offspring arising from the second matings of the P0 and P1 generations did not exhibit any adverse dose-related effects with respect to developmental landmarks including milk in stomach (days 0, 4, 7), detached pinna, incisor eruption, eye opening (Tables 81 to 84, pp. 164 to 169).

D. Macroscopic Findings in Pups

Macroscopic data of F1B and F2B pups exists for 1) pups found dead before weaning, 2) pups culled on day 4, 3) pups at weaning (Study Director), and 4) pups at weaning (pathology): Appendices 80 to 83 (pp. 895A to 926A) for F1B pups and Appendices 84 to 87 (pp. 927A to 950A) for F2B pups.

Generally speaking with respect to both F1B and F2B pups there were no definitive findings indicating a teratogenic or birth defects problem. Frequently observed phenomena in the control and dosed animals were convoluted and dilated ureters and dilated renal pelvis. However, there is no evidence that SC-0224 enhanced the frequency of those abnormalities.

Females: Whole body weight was numerically but not significantly reduced in the high-dose group. The only organ weight significantly reduced in the high-dose group was that of the spleen. The effects of lower doses on body weight and absolute organ weights were unremarkable (Table 92, pp. 182 and 183).

G. Relative Organ Weights, F1B and F2B Weanlings

The only remarkable findings were: 1) significantly increased brain weight at the high dose in F1B and F2B males and F1B females, and 2) a remarkable repression in relative spleen weight in all dose groups among F2B males and in the high-dose F2B female group, tabulated as follows:

Relative Spleen Weight (%), F2B Generation Weanlings

	<u>Control</u>	<u>150 ppm</u>	<u>800 ppm</u>	<u>2000 ppm</u>
Male	0.676	0.499*	0.504*	0.434*
Female	0.534	0.473	0.470	0.423*

*Significantly different from control, $P < 0.05$, two-tailed.
(Table 90, pp. 178-179 and Table 94, pp. 186-187).

III. GENERAL FINDINGS IN F2B ADULT MALES

A. Clinical Observations

There were no remarkable observations in any dose group (Table 95, p. 188).

B. Body Weights

There was, for the high-dose group, a general repression of body weight increase of F2B generation animals, as evidenced by significant weight reductions relative to controls over a 55-day observation period. Weight gain in other dose groups was not so impaired (Table 96, p. 189).

C. Feed Intake

Feed intake was diminished in the high-dose group only, a finding consistent with reduced body weight gain for this groups (Table 97, p. 190), as evidenced by feed efficiency data (Table 98, p. 191).

E. Organ Weights

Absolute organ weight data do not indicate any effects on females which could be viewed as related to the administration of SC-0224 (Table 112, pp. 210 to 212). The same statement is applicable for Relative Organ Weight Data (Table 113, pp. 213 to 215).

F. Clinical Findings

Among hematological parameters, platelet count data suggest a dose response effect (as was noted for males): control control(863), 150 ppm(899), 800 ppm(1042) and 2000 ppm(1107). See note p. 19. Platelet counts ($10^3/\text{mm}^3$) by our calculations were significantly elevated in the high- and middle-dose groups. (Table 114, p.216)

Among blood chemistry values, BUN was significantly reduced for the mid- and high-dose groups, as were total protein and albumin.

Mean protein electrophoretic data indicated significantly reduced total protein in the mid- and high-dose groups (Table 116, p. 219).

Summary of Findings

Body weight gain for both male and female, P0 and P1 generation, rats was impaired by doses of SC-0224 as low as 800 ppm in the diet. Organ weight reductions among P0 and P1 rats were also observed at 800 ppm. Most notably affected in this manner were thymus, liver, heart, and kidneys. During gestation, food intake for P0 and P1 animals was less at 800 ppm. Similarly, during lactation, weight gain and food intake for P0 and P1 animals were less in the 800 ppm dosed animals.

Weight gain of P0 and P1 pups during the 21-day postpartum period was reduced in groups feed 800 ppm.

At scheduled sacrifice of F1B weanlings, body weight and organ weights were reduced in the 2000 ppm dose group. Similarly, F2B body weights were reduced in the high-dose group, but male spleen weight was significantly reduced in the 800 ppm dose group, otherwise, organ weights for both sexes were affected by 2000 ppm.

A notable finding for F2B weanling animals, under relative organ weights, was that in male rats of decreased spleen weight, LOEL < 150 ppm. For F2B females, spleen LOEL = 2000 ppm, with a trend toward lower spleen weights at the lower dose levels.

Evaluations on F2B adult rats revealed the following:

serious defect, this is not viewed as exceeding the incidence likely to occur spontaneously.

Necropsy of F2B adult rats did not disclose any remarkable defects.

In terms of such parameters as mating index and fertility index for males and females, and gestation index, behavior during nursing, length of gestation and length of delivery, there were no adverse dose-related effects observed with respect to P0 and P1 matings.

Overall Reproductive NOEL = < 150 ppm (F2B, male, weanlings
relative spleen weight reduction)

Overall Clinical NOEL = 150 ppm (platelet count increase,
male and female adult F2B generation)

Core Rating = Supplementary

Repairability = Nonrepairable

Reference:

Raab, S.O. The spleen and reticuloendothelial system.
(1974) In: Pathologic physiology, mechanisms of
disease. W.A. Sodeman, Jr., and W.A. Sodeman, eds.
W.B. Saunders, Co., PA.

Note (as referenced on pp. 16 and 17): combined F2B adult male and female platelet count data revealed statistically significant reductions ($P < .05$) in the middle and high dose groups.

anesthetized with sodium pentobarbital and sacrificed by exsanguination. The following tissues were examined at necropsy, and portions retained in formalin for future reference: trachea, larynx, bronchi, nasal passages, lungs, liver, spleen, kidneys, adrenals, heart and any tissues appearing abnormal.

During the period of 4-hour exposure to the test material, atmospheric aerosol concentrations were determined periodically, at 30-minute intervals. In addition, particle size analyses were performed at the 55- and 170-minute time points during the exposure period. This determination involved the use of low-volume cascade impactors.

The nominal concentration of test material in the chamber test atmosphere, indicated above to be 0.81 mg/L, is a calculated figure derived from the ratio of amount of test material used during the exposure to the total chamber air flow during this period.

Results:

As indicated previously, the mean concentration \pm S.D. of the test material in the exposure chamber as determined by gravimetric means was 0.81 ± 0.42 mg/L (0.45 mg ai/L, as calculated based on 56.2% purity).

Measurement of aerosol particle size as determined at the 55- and 170-minute exposure time points were, in terms of mass median aerodynamic diameter (MMADar) and geometric standard deviation (σ), 2.5 ± 2.75 μ m and 2.0 ± 2.36 μ m, respectively.

Conclusion: At the highest achievable concentration of 0.81 mg/L of SC-0024, there were no deaths recorded. Only a few transient clinical signs were observed.

Core: Guideline.

11

sham exposure. (Would be curious to know whether anything such as water or emulsifier was or should have been used.)

Animal body weights were recorded on day 0 (day of initial exposure) and on days 2, 7, and 13. The body weights of all nonscheduled deaths were obtained immediately before necropsy. After 14 days of observation, animals were anesthetized with sodium pentobarbital and sacrificed by exsanguination.

During the 4-hour exposure periods to the test material, atmospheric aerosol concentrations were determined periodically, at 30-minute intervals, except for the high-dose group which was sampled more frequently. In addition, particle size analyses were performed at approximately 1 and 3 hours into the experiments. The determination involved the use of low-volume cascade impactors.

The nominal concentrations of test material in the chamber test atmosphere in the various studies were calculated values derived from data obtained gravimetrically. In particular, under each set of exposure conditions a known volume of chamber air was filtered, residue weighed and concentration of test material in the atmosphere calculated and reported as grams/liter.

Results:

The calculated concentrations of SC-0224 4LC in the various studies were reported as 0.61, 1.30, 1.58, and 1.60 mg/L. The study author notes that "The test material in the generator reservoir became too foamy to use after a short period and had to be replaced several times during each exposure. This made the nominal concentrations artificially high and they had no relationship to actual measured exposure levels" (Page 5).

The mass median aerodynamic diameters (MMADar) in the various studies ranged from 1.68 μm to 3.10 μm , with geometric standard deviations ranging 1.90 μm to 2.22 μm . A stable particle size was reportedly achieved in each study.

General Animal Observations:

As observed during the exposure, the animals were described as "Lethargic with stained muzzles, some tearing and signs of labored breathing" (p. 6). Mortality was high, particularly among males, following exposure. Most deaths occurred during the first 2 days postexposure. Mortality for males was 80 percent in the two high-dose groups, 50 percent in the next to lowest dose group and 0 percent in the low-dose group, the LC₅₀ being 1.30 mg/L. Mortality for females in the various dose groups was from high to low dose 60, 50, 10 and 0 percent. LC₅₀ = 1.56 mg/L for females.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

005690

JAN 27 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCESMEMORANDUM

SUBJECT: Review of SC-0224 Two-Generation Reproduction
Study in Rats, Addendum I: Response to EPA
Comments Submitted by Stauffer Chemical Company.
EPA Reg. No.: 476-2225/476-2226
TOX Chemical No. 893C

TO: Robert Taylor, PM 25
Herbicide/Fungicide Branch
Registration Division (TS-767)

FROM: Brian Dementi, Ph.D. *Brian Dementi, 1/22/87*
Review Section #1
Toxicology Branch/HED (TS-769)

THRU: Robert B. Jaeger, Section Head *RMJ 1/21/87*
Review Section #1
Toxicology Branch/HED (TS-769)

Applicant: Stauffer Chemical Company
1200 S. 47th Street
Richmond, CA

Stauffer Chemical Co. has provided a company response to questions raised in our 5/30/86 review (Dementi) regarding the 2-generation reproduction study. TOX Branch concluded in that review that no NOEL had been established, on the basis of finding reduced relative spleen weight in F2B weanling males at the lowest dose level of 150 ppm. A NOEL for increased platelet count in F2B adults (M,F) was estimated at the lowest level administered (150 ppm). Additionally, TOX Branch noted a statistically significant reduction in thymus weight (absolute and relative) for F2B adult males at 2000 ppm. In view of these effects, TOX Branch expressed concern that SC-0224 may be exerting an adverse effect on the reticuloendothelial system.

In the present submission, Stauffer provides results of additional study and suggests that these data support their previous conclusion that a NOEL of 150 ppm was established.

The following responses are provided for each concern raised in our 5/30/86 review:

I. Reduction in Relative Spleen Weight

Stauffer claims that statistically significant decreases in relative spleen weight which were evident at 150, 800 and 2000 ppm in F2B weanling males is attributed to atypically elevated mean absolute spleen weight and low mean body weight for the control animals. Stauffer compared spleen weights of F1B and F2B weanling males and females to help illustrate this point.

Absolute Spleen Weight, Grams

<u>Group</u>	<u>F1B</u>		<u>F2B</u>	
	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>
Control	.329	.315	.474	.354

Spleen weights of F2B males are numerically greater than F1B males, and except for F2B males the other control values are comparable to absolute spleen weights of the Low Dose group.

Furthermore, Stauffer argues that body weights of control F2B weanlings (M,F) were relatively low, perhaps due to increased litter size of this group:

Body Weight, grams

<u>Group</u>	<u>M</u>	<u>F</u>
Control F1B Weanlings	78.9	79.3
" F2B "	70.2	66.6

In addition to these data purporting to explain the reduced relative spleen weights in the various dose groups, Stauffer provided additional data on body weights and spleen weights of control animals. In 50 weanling male rats having a mean body weight of 81.8 grams (a figure comparable to F1B weanling mean weight of 78.9 grams), the mean spleen weight was 0.339 grams. This figure does support Stauffer's position that a mean spleen weight of 0.474 grams in rats of comparable size is unusually high. Consequently, a relative spleen weight of 0.418 as derived

from the supplemental spleen and body weight data appears to be a more reliable control value than that reported for weanling F2B male controls (0.676) in the original study.

TOX Branch is satisfied that Stauffer has adequately addressed this concern and that SC-0224, at doses evaluated in the previous study, did not exert an adverse effect on spleen weight at 150 ppm.

II. Thymus

In our previous review we noted that for F2B male adults, absolute and relative thymus weights were reduced, being statistically significant at the high dose.

The Registrant has tabulated thymus weight changes for the different generations at the various dose levels. Statistically significant absolute thymus weight decreases are noted for P1 (M,F) at 800 and 2000 ppm and for P0 (M), F1B weanlings (F) and F2B (M) adults at 2000 ppm. When expressed on a relative weight basis, the only significant decreases were for groups P0 (M), P1 (F) and F2B adult (M) at the 2000 ppm dose level.

TOX Branch agrees with the Registrant that a NOEL = 150 ppm has been demonstrated for thymus weight changes in this study.

III. Platelet Counts

In our review of the original 2-generation study, TOX Branch identified significant increases in platelet count at 800 and 2000 ppm in both sexes of F2B adults. (Appendices 103, 114)

<u>ppm Level</u>	<u>Males</u>	<u>N</u>	<u>Females</u>	<u>N</u>
0	855 + 169	5	863 + 87	5
150	888 + 65	5	899 + 178	5
800	1017 + 69	5	1042 + 49	5
2000	1092 + 68	4	1107 + 162	5

In Addendum I, Stauffer provided historical platelet count control data for male and female rats in the age groups 1-3 months and 4-14 months, and notes that all of the platelet values for animals in the 800 and 2000 ppm dose groups fall within the reference range for the laboratory. Furthermore, Stauffer emphasizes that one of the male reference ranges used has a skewed distribution. The petitioner also points out

that the study controls appear to be atypical and that this particular group of controls is derived from the same group of animals in which the atypical spleen weights were observed. For these reasons Stauffer would have the Agency accept that an apparent dose related increase in platelet count in both sexes has no biological significance.

Tox Branch adheres to the conclusion reached in our original review that the increases in platelet count observed in both sexes at 800 and 2000 ppm are significant. Therefore NOEL=150 ppm for this biological effect. Since platelet count was altered at the higher doses and there is uncertainty as to what dose represents the LOEL, any additional studies which include assessments of this and/or related parameters should be carefully evaluated.

TOX Branch conclusions: NOEL = 150 ppm, LOEL = 800 ppm
[reduced feed intake and body weight in both parents and pups;
reduced absolute thymus weight, P1 (M,F); platelet count increase,
F2B adults (M,F)]

Core rating: upgrade from supplementary to guideline